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Ovarian response in preimplantation genetic testing for myotonic dystrophy type 1

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Keywords:

Ovarian stimulation; Ovarian response; Ovarian sensitivity; Preimplantation genetic testing (PGT-M); Myotonic dystrophy type 1 (DM1; Steinert).

Abstract

Purpose:

To evaluate ovarian stimulation response in couples undergoing preimplantation genetic testing (PGT-M) for myotonic dystrophy type 1 (DM1) METHODS: Retrospective, observational, multicentric study. Parameters of ovarian response and PGT-M outcomes were compared according to the DM1-affected patient (female or male). A total of 229 couples underwent at least one controlled ovarian hyperstimulation cycle for the PGT-M procedure. Overall, 678 COS cycles were started, leading to 560 cycles with oocyte retrievals and subsequent PGT-M analysis.

Results:

At the time of the first PGT-M attempt, affected DM1 females were 1 year older and their serum AMH level was significantly lower than that of the healthy partner of affected DM1 males. After higher starting and total doses of exogenous gonadotropins, the number of mature oocytes was not statistically different between both groups (9 [6-13] vs 9 [6-13] mature oocytes, $p=0.73$). The FORT index was similar in both groups (35.2% [19.2-52.8] vs 33.3% [19.6-50.0], $p=0.09$), suggesting that antral follicle responsiveness to FSH is not altered. The live birth rate per fresh embryo transfer was 23.8% in the affected females group and 27.6% for the affected males.

Conclusion:

After adapted controlled ovarian stimulation protocol and starting dose, a similar response (number of mature oocytes) and sensitivity (FORT index) was observed in DM1 females when compared to healthy partners of DM1 males undergoing PGT-M.

Myotonic dystrophy type 1 (DM1) or Steinert's disease is a neuromuscular genetic disorder that follows an autosomal dominant transmission pattern [1]. DM1 represents the most common form of adult muscular dystrophy [2]. Different phenotypes of the disease exist [3]. Congenital myotonic dystrophy is the most severe form of the disease [4]. The common form of the disease is dominated by myotonia and muscles weakness with a prognosis mainly depending on cardiac and respiratory symptoms. Patients with DM1 are reported to have reduced fertility, especially affected males [5–7]. However, the association between female fertility, ovarian reserve, and DM1 remains controversial [8–10].

Before conceiving, couples usually benefit from preconception counselling with the possibility of either prenatal or preimplantation diagnoses. Preimplantation genetic testing for monogenic disease (PGT-M) is an assisted reproductive technique aiming to genetically screen embryos created *via in vitro* fertilization prior to transferring unaffected embryos into the uterine cavity. Evidence indicate that the number of mature oocytes retrieved after controlled ovarian stimulation (COS) represents a key parameter of PGT success since it is directly related to the number of embryos available for biopsy and the chances of obtaining healthy and viable embryos [11]. However, since cohorts are scarce, few studies report COS outcomes in females with DM1, and the results are conflicting. Some suggest lower ovarian reserve and poorer ovarian response [9, 10], or reduced sensitivity to gonadotropin stimulation [12], while others find no significant differences [8, 13]. More research is needed to clarify the impact of DM1 on COS outcomes.

To clarify this issue, we performed a multicentric investigation which aimed to compare COS outcomes between DM1 females and healthy partners of DM1-affected males having undergone PGT-M.

Methods

We conducted a multicentric, retrospective, national observational study encompassing all centers authorized for PGT-M in our country. As a reference, screening for aneuploidies (PGT-A) is not permitted under our national law.

Patients

All couples, with one member affected with DM1, having undergone at least one COS cycle for PGT-M in these centers between January 2006 and December 2019, were included in the present study. Before inclusion in the PGT-M program, feasibility of the procedure was determined through assessment of ovarian reserve including anti-Müllerian hormone (AMH) dosage and antral follicle count (AFC) by ultrasonography, and a semen analysis for males. As a standard, an AMH level greater than 1 ng/ml is required at the time of the PGT-M request, along with a corresponding AFC (typically exceeding 10). Moreover, females with DM1 should have received an agreement for pregnancy from a multidisciplinary team (at least from the cardiologist and the neurologist) when needed. All women with a contraindication to ovarian stimulation or pregnancy were excluded.

All male patients were excluded if surgical sperm (fresh or frozen) was required to allow for a clearer assessment of embryo and pregnancy rates for the study purpose, as severe male factor infertility could disproportionately affect these outcomes and confound the results.

COS protocols and PGT-M procedure

Ovarian stimulation was achieved using a long GnRH agonist or antagonist protocol according to each center's routine practice, international recommendations, and the timing of treatment. COS protocol and initial dose of gonadotropins were based on females' age, AFC, AMH, body mass index (BMI), and considering previous ovarian stimulation outcomes if any. COS were monitored by transvaginal ultrasound and serum measurements of estradiol (E2), progesterone (P4), and luteinizing hormone (LH) levels. Ovulation was triggered with human chorionic gonadotropin (hCG) and/or GnRH agonist (triptorelin, 0.2 mg sc) injection administered when at least three or four pre-ovulatory follicles (16–22 mm in diameter) were observed. Oocytes were retrieved 36–40 h after triggering by transvaginal ultrasound-guided aspiration under local or general anesthesia.

PGT-M procedure

Cumulus-oocyte complexes (COCs) recovered were denuded and the metaphase II oocytes (MII) were inseminated by intracytoplasmic sperm injection (ICSI). Fertilization was checked after 24 h, and embryo biopsy was scheduled at the cleavage or blastocyst stage using a laser procedure. Cleaved embryo morphology was graded according to number, size, and uniformity of blastomeres, degree of fragmentation, and the presence of multinucleated blastomeres. Cleaved embryo quality was insufficient for embryo biopsy if there were less than six blastomeres on day 3 (18). At D5, blastocyst morphology was evaluated according to the Gardner and Schoolcraft grading system (19).

Genetic analysis was performed according to each center's practice. Embryos carrying the mutant allele were diagnosed as affected and were excluded from transfer. When available, one or two unaffected embryos were transferred into the uterus on day 4 or 5 after ICSI. Supernumerary and good-quality unaffected embryos were cryopreserved by either slow freezing or vitrification, according to the time of the PGT-M procedure. Blood test for pregnancy was performed 10–15 days after embryo transfer and if positive, ultrasound was scheduled 4–6 weeks later to confirm the pregnancy localization and evolution.

Studied variables

Females' characteristics and ovarian reserve markers at the first COS cycle were collected retrospectively from medical files. COS outcomes were assessed by the total dose of exogenous gonadotropin, duration of ovarian stimulation, maximal E2 at the end of COS, and the total number of retrieved oocytes. In addition, follicular responsiveness to FSH was assessed by the follicular output rate (FORT) index calculated from the ratio between the number of preovulatory follicles measuring 16–22 mm in diameter on the day of ovulation trigger $\times 100/\text{AFC}$. PGT-M outcomes were evaluated by the number of biopsied embryos and the number of cycles with at least one healthy embryo to transfer. Clinical pregnancy was defined by the presence of a fetal heartbeat at 6–7 weeks of pregnancy.

Statistical analysis

COS outcomes were compared between females presenting with DM1 or the healthy partners of DM1-affected males. The results are presented as mean \pm standard deviation (SD) distributions. For statistical comparisons of females' characteristics, COS and PGT-M outcomes, Student's *t* test or Mann–Whitney when appropriate was used for continuous variables and chi-square test for categorical variables. Taking into account the center effect might influence the results, we also performed multivariate analysis adjusted on the center and the female age with a generalized mixed model with the center as a random effect and age as a fixed factor. Both results' *p* values are presented in the tables for main outcomes. All statistical tests were two-sided, and a *p* value <0.05 was considered statistically significant.

Ethical approval

Consent for the use of their medical data for research purpose was obtained from all patients/couples at the time of the PGT-M attempt. An Institutional Review Board approval was obtained for this retrospective study (CEROG-2020-GYN-0603).

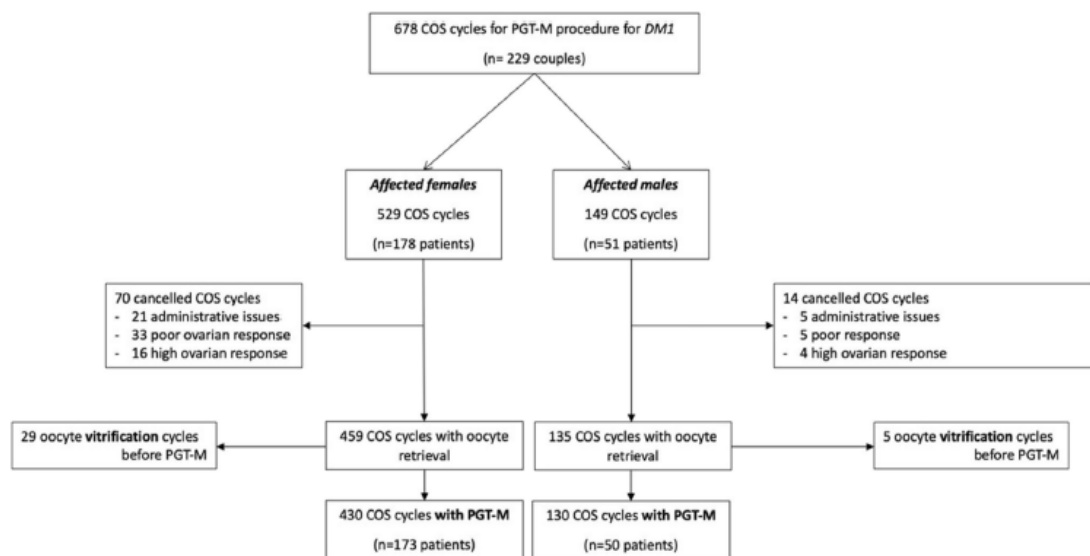


Figure 1 Flowchart of the study. *COS*, controlled ovarian stimulation; *PGT-M*, pre-implantation genetic testing for monogenic disease; *DM1*, myotonic dystrophy type 1

Results

Throughout the study period, 229 couples started at least one COS cycle for PGT-M (Figure 1). The number of couples included in each PGT center varied between 9 and 70 and the number of COS cycles leading to oocyte pick-up ranged between 19 and 149 (for details, see Supplemental Table 1). Among couples, DM1 pathogenic variant was carried by the female or the male in 178 and 51 cases, respectively. Among the 678 COS cycles started, 459 led to an oocyte retrieval in affected females and 135 in the partners of affected males. A total of 84 cycles were cancelled, mainly in females suffering from DM1 ($n=70$ cycles) (Figure 1).

Table 1 COS outcomes according to the affected partner

	DM1-affected female (n=459 cycles)	Healthy partners of DM1-affected male (n=135 cycles)	p°	$p^{\circ\circ}$
Age (years)	32.9±3.8	31.8±3.6	0.004	
BMI (kg/m ²)	21.6 [19.6–24.0]	21.1 [19.6–23.5]	0.7	
AMH (ng/ml)	2.75 [1.71–4.08]	3.80 [2.60–5.15]	<0.001	
AFC (follicles)	16 [12–22]	16 [12–21]	0.9	
Smoking, n (%)	73/318 (18.7%)	27/119 (22.7%)	0.3	
Protocol			0.08	
Agonist	161 (37.8%)	56 (46.7%)		
Antagonist	265 (62.21%)	65 (53.3%)		
Starting FSH dose (IU)			0.01	
≤150	113 (27.5%)	48 (42.5%)		
[150–300]	145 (35.3%)	33 (29.2%)		
≥300	153 (37.2%)	32 (28.3%)		
Total dose of FSH (IU)	2250 [1594–3075]	2025 [1312–2825]	0.01	
Duration (days)	10 [10–12]	10 [9–11]	0.07	
Maximal estradiol (pmol/l)	2560 [1742–3469]	2448 [1602–3381]	0.41	
FORT (%)	35.2 [19.2–52.8]	33.3 [19.6–50.0]	0.09	0.31
Retrieved oocytes	12 [8–16]	11 [8–16]	0.63	0.65
Mature oocytes	9 [6–13]	9 [6–13]	0.76	0.63
	DM1-affected female (n=430 cycles)	Healthy partners of DM1-affected male (n=130 cycles)		
Cleaved embryos	7 [4–10]	6 [4–10]	0.78	0.56

Mean±SD or median [25p–75p]

p° , Mann-Whitney test or Student *t*-test; $p^{\circ\circ}$, multivariate analysis adjusted on the center and the female age with a generalized mixed model with the center as a random effect and age as a fixed factor

FORT (follicular output rate) = follicles ≥ 16–20 mm on dhCG × 100/AFC at the beginning of COS

COS outcomes

Comparison of ovarian response to stimulation between females with DM1 and healthy partners of affected males is reported in Table 1. Overall, age at the beginning of ovarian stimulation was significantly higher in affected females than in healthy partners of DM1 males (32.9±3.8 vs. 31.8±3.6 years, $p=0.004$). BMI and AFC were not statistically different between the groups, whereas serum AMH level was significantly lower in affected females (2.75 [1.71–4.08] vs. 3.80 [2.60–5.15] ng/ml; $p<0.001$).

Despite higher starting and total doses of exogenous gonadotropin administered, DM1 females had similar parameters of ovarian response to COS as healthy partners of DM1 males. Hence, numbers of retrieved and mature oocytes per cycle were not statistically different between both groups (12 [8–16] vs. 11 [8–16] retrieved oocytes, $p=0.63$, and 9 [6–13] vs. 9 [6–13] MII, $p=0.73$, for affected females and healthy partners of affected males, respectively). These results remained unchanged after adjustment for ART center and female age using the generalized linear mixed model. Among the 459 oocyte pick-up, only four had no COCs at oocyte retrieval and only two had solely immature oocytes. All of them were DM1 females.

PGT-M results per cycle

In the group of DM1 females, 75.8% (326/430) of oocyte retrieval led to embryo biopsy and a median of 4 [3–7] embryos were biopsied per cycle. In the group of healthy partners of DM1 males, 83.1% (108/130) of oocyte retrieval led to embryo biopsy and a median of 4 [3–7] embryos were biopsied per cycle (non-significant p -value). The proportion of started cycle resulting in the obtention of at least one unaffected embryo was 58.6% (252/430) in the group of DM1 females and 70.4% (92/130) in the group of healthy partners of DM1 males ($p<0.01$).

A fresh embryo transfer was performed in 49.7% (214/430) and 58.5% (76/130) of the started cycles for affected females and healthy partners of affected males. These results were not significantly different between the two groups.

Pregnancy outcomes

Clinical pregnancy and live birth rates per fresh embryo transfer were 29.4% (63/214) and 23.8% (51/214) in DM1 females vs 40.7% (31/76) and 27.6% (21/76) in healthy partners of DM1 males. These results were not significantly different between the two groups.

Overall, 33.2% of the entire cohort (76 couples) achieved at least one live birth after a minimum to 1 and a maximum of 8 embryo transfers. A total of 95 babies were born. In females with DM1, 30.9% ($n=55$) had at least one live birth from PGT-M, 56 babies were born after fresh embryo transfer and 11 after frozen thawed embryo transfer. Twelve couples had two babies born (resulting from a twin pregnancy for five couples). In couples with the affected male, 41.2% ($n=21$) had at least one live birth and 28 babies were born (23 after fresh embryo transfer and five after frozen thawed embryo transfer). Among them, seven couples had two babies after PGT-M (resulting from a twin pregnancy for two couples).

Discussion

The aim of this multicenter retrospective study was to evaluate ovarian response to COS in DM1-affected females included in a PGT-M program. For this, we compared COS outcomes in DM1-affected females to healthy females whose male partners were affected by DM1. At the time of the first PGT-M attempt, DM1 females were 1 year older than controls and their serum AMH level was significantly lower, leading to a stimulation using higher starting and total doses of exogenous gonadotropins. However, the number of retrieved and mature oocytes was comparable in both groups of patients. After adjustment for center and females' age, all results remained unchanged, excluding a center effect.

We found significantly lower serum AMH levels in females affected by DM1, even after adjustment for patient's age. Our results are in accordance with other studies that evaluate ovarian reserve markers in DM1 female candidates for PGT-M [10, 14]. However, these results should be interpreted with caution as females included in PGT-M programs are often selected upon ovarian reserve parameters and severity of the symptoms. Indeed, only DM1-affected females with a low severity and without contraindication to pregnancy may be included. Recently, Parmova et al. first analyzed AMH in the most common muscular dystrophies. They found a significant difference in serum AMH levels between 21 females affected by DM1 (18–44 years old) and a control group composed of healthy women in the same age range after adjustment for age [15]. It would be interesting to investigate whether DM1 directly affects ovarian function and if so, with differences according to the severity of the disease. This point is important to improve patients' knowledge and improve their counselling especially on the possible indication of oocyte vitrification to keep those at risk of decreased ovarian reserve, eligible for PGT-M. From a pathophysiological point of view, it has been hypothesized that RNA of mutated Myotonic Dystrophy Protein Kinase (DMPK) accumulates into granulosa cells and alters their function [10]. Besides, the expression of the

SIX5 gene located near DMPK would be lower in patients with DM1. If the absence or the decrease of SIX5 expression causes anomalies in spermatogenesis [16], its implication on females' gonadal function remains unknown, making this gene a candidate for investigation. Although ovarian reserve and ovarian stimulation protocols were different between the two groups with significantly higher initial and total gonadotropin doses in DM1-affected females, we failed to find any difference on COS outcomes between DM1-affected females and healthy partner of DM1 males, even after multivariate analysis adjusted for the center of care and age. These results are in accordance with previous studies [12, 13, 17], whereas others found a lower number of mature oocytes in DM1-affected females when compared to controls [8–10] (Table 2). In addition to the number of retrieved and mature oocytes, we analyzed the FORT index, an efficient quantitative and qualitative marker of ovarian responsiveness to gonadotropins [18]. This index was similar in DM1 females and healthy controls, suggesting that while DM1 impacts ovarian reserve, antral follicle responsiveness to FSH is not altered. This finding contradicts previous suggestions based on a much smaller patient cohort [12].

Table 2 Comparison of different studies of the response to ovarian stimulation in patients with DM1

Studies	Number of patients/cycle	Control group	Total FSH (UI)	Total duration of stimulation (days)	Oocytes MII	Embryos biopsied	Clinical pregnancy rate per fresh embryo transfer
(Feyereisen <i>et al.</i> 2006)	22 (44)	X-linked disorders	2787.5 vs 2100 $p=0.009$	Not studied	10.5 vs 13 NS	4.5 vs 6 $p=0.03$	Not studied
(Sahu <i>et al.</i> 2008)	15(21)	Partner of patients with sperm abnormalities requiring ICSI	53.69 vs 35.51 $p<0.001$	11.46 vs 10.67 $p<0.01$	10.5 vs 11.26 NS	Not studied	Not studied
(Verpoest <i>et al.</i> 2008)	54 (205)	Partner of DM1-affected and X-linked disorders	2789.6 vs 2373.4 $p=0.23$	11.4 vs 11.7 $p=0.61$	10.4 vs 12.2 vs 11.3 NS	5.4 vs 6.3 vs 6.8 NS	29.4% vs 38.1% vs 31% NS
(Dechanet <i>et al.</i> 2010)	17 (33)	X-linked disorders	2244 vs 1841 $p=0.07$	10.8 vs 10.2 $p=0.08$	12.9 vs 12.2 $p=0.51$	4.1 vs 4.6 $p=0.74$	35.7 vs 31 $p=0.99$
(Srebnik <i>et al.</i> 2014)	21(57)	X-linked disorders	6198 vs 3697 $p<0.0001$	12.2 vs 10.3 $p<0.0001$	10.4 vs 17.4 $p<0.0001$	Not studied	28.6% vs 43.5% NS
(Fernández <i>et al.</i> 2017b)	22 (33)	Partner of DM1-affected males and A-hemophilia	Not studied	Not studied	8.7 vs 10.5 vs 13.6 NS	3.3 vs 5.1 vs 6.8 NS	25% vs 33.3%vs 26.9% NS
Our study (median or %)	178 (430)	Partner of DM1-affected males	2250 vs 2025 $p=0.01$	10 vs 10 $p=0.07$	9 vs 9 $p=0.76$	4 vs 4 $p=0.4$	29.4% vs 40.7% $p=0.07$

If the main objective of the present study was to assess ovarian response to COS, we also analyzed PGT-M results for DM1. We found that the proportion of cycles without biopsied embryo was significantly higher in DM1 females, essentially due to poor embryo quality. These results suggest that the disease might impact embryo quality in affected females. Alternatively (or conjointly), the decrease in embryo quality could also come from a poorer oocyte quality correlated with the higher hormonal doses used for the COS of DM1 subjects. In a previous single-center study, the rate of lower quality embryos (grade D in Gardner's classification) was significantly higher in the women-affected group [8]. Overall, about half of initiated COS cycle allows an embryo transfer in both groups, but the proportion of cycles with at least one unaffected embryo available for transfer was significantly decreased in affected females. Finally, the clinical pregnancy rate as well as the live birth rate was comparable in both groups.

We report here the largest study investigating COS outcomes in DM1 patient's candidates for PGT-M (Table 2). We decided to design a study specifically based on PGT-M candidates, including either DM1-affected females and the healthy partner of DM1-affected males as controls. The use of such a control group allows the comparison with healthy females and avoids another selection bias. Nevertheless, as maternal transmission results in more severe forms and a higher frequency of congenital forms with neonatal death than paternal transmission [19, 20], couples with DM1-affected females are more prone to ask for PGT-M when compared to couples with affected males. Thus, the number of females in the study group was higher than in the control group, which could have also influenced our results and could reduce the statistical robustness of the study. Nevertheless, although the choice of the control group enables analysis of the results on embryos, we are aware that DM1-affected males may suffer from spermatocytic abnormalities often requiring ICSI [7]. Another major limitation comes from the retrospective nature of study and the long inclusion time due to the low prevalence of this pathology as practices evolved over time not only in terms of ovarian stimulation protocols but also regarding IVF laboratory techniques or PGT-M techniques and practice such as day of embryo biopsy, number of cells biopsied, and embryo transfer policies. Moreover, the multicenter design of this study induces biases but those were accounted for in the statistical analysis.

At least, our study provides new and relevant information concerning the overall result after PGT-M for DM1. In our study, 33.2% of the entire cohort had at least a healthy baby at the end of the PGT-M process. This result is in accordance with published data looking at the results of PGT-M which found a cumulative live birth rate ranging from 28.6 to 48.9% [21, 22]. In 2021, The ESHRE PGT Consortium published its data collection finding a live birth rate of 24% between 2013 and 2015 [23]. The live birth rates following PGT-M for DM1 reported in our study could likely be improved by exclusively using blastocyst-stage biopsies, as cleavage-stage biopsies—widely used in this retrospective cohort—have been shown to impair implantation [24]. Despite the fact that PGT-M avoids medical abortion of a spontaneous pregnancy bearing an affected child, IVF with PGT-M can be a long and stressful experience. Moreover, the process of PGT could be extremely impractical and psychologically demanding, especially for couples who had unsuccessful attempts and remained childless after PGT-M representing 66.8% of our entire cohort. Unsuccessful PGT-M procedures can have long consequences for emotional well-being. Survey studies of couples who had unsuccessful PGT demonstrate that the psychological effects of the process remain present for up to 3 years after the attempt [25]. This study reports real-life data and provides couples with clear and precise information on the chances of live birth in this specific situation.

In conclusion, we report the first national multicenter study including a large cohort of couples with one of the partners affected with DM1, candidates for PGT-M. Our findings indicate that although the ovarian reserve could be impacted by DMPK pathogenic variant, the ovarian response to COS is not altered in DM1-affected females if the exogenous FSH starting dose is individualized. In light of these results, oocyte vitrification for DM1 females before PGT-M process could be discussed with the patients. Moreover, we showed that PGT-M leads to live birth rates for 30.9% for DM1 females and for 41.2% for healthy partners of affected males. These results are useful to advise couples before they enter a PGT-M program.

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Author contribution

CS: study design, collection of data, statistical analysis and interpretation of data; writing of the manuscript; NR: writing of the manuscript; MGu: study design, collection of data, writing of the manuscript; TA, CM, CR, AR, FL, OP, AG, PR, GM: collection of data and critical revision of the manuscript; JS, AM: study design, critical revision of the manuscript; MGr: study design, analysis and interpretation, critical revisions of the manuscript.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest The authors declare no competing interests.

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